Impact of positron emission tomography - computed tomography status on progression-free survival for relapsed follicular lymphoma patients undergoing autologous stem cell transplantation

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Abstract

The optimum management approach for patients with relapsed or refractory follicular lymphoma remains uncertain. Autologous stem cell transplantation (autoSCT) is considered a standard option in suitable, younger patients with relapsed follicular lymphoma. AutoSCT is associated with very durable remissions in a minority of subjects, but also with significant, well-established toxicities. Although positron emission tomography (PET) status prior to autoSCT is an established prognostic factor in diffuse large B-cell lymphoma and Hodgkin lymphoma, no data exist in follicular lymphoma. We describe survival outcomes according to pre-transplant PET status, classified by the Lugano criteria into complete metabolic remission (CMR) *versus* non-CMR, in 172 patients with relapsed or refractory follicular lymphoma within a national, multicenter, retrospective British Society of Blood and Marrow Transplantation and Cellular Therapy registry study. The median number of lines of therapy prior to SCT was three (range, 1-6). The median follow-up after SCT was 27 months (range, 3–70). The median progression-free survival for all patients after autoSCT was 28 months (interquartile range, 23-36). There was no interaction between age at transplantation, sex, number of months since last relapse, Karnofsky performance status or comorbidity index and achieving CMR prior to autoSCT. Superior progression-free survival was observed in 115 (67%) patients obtaining CMR *versus* 57 (33%) non-CMR patients (3-year progression-free survival 50% *vs.* 22%, *P*=0.011) and by pre-SCT Deauville score (continuous variable 1-5, hazard ratio [HR]=1.32, *P*=0.049). PET status was independently associated with progression-free status (non-CMR HR=2.02, *P*=0.003), overall survival (non-CMR HR=3.08, *P*=0.010) and risk of relapse (non-CMR HR=1.64, *P*=0.046) after autoSCT by multivariable analysis. Our data suggest that pre-SCT PET status is of clear prognostic value and may help to improve the selection of patients for autoSCT.

Introduction

Follicular lymphoma (FL) is the most common indolent B-cell non-Hodgkin lymphoma with a relapsing and remitting natural history that typically spans many years. High-dose chemotherapy and autologous stem cell transplantation (autoSCT) has been considered a treatment option for young, fit patients (usually <70 years old) for a number of decades, although uptake of this approach is somewhat variable across the globe,[1] and is most often now reserved for those with relapsed or refractory (R/R) FL.[2] Recent evidence has helped to further determine the efficacy of this approach, particularly in high-risk patients, defined by the duration of the first remission being <24 months, i.e., pro-

gression of disease within 24 months (POD24).[3,4] Published series document that a significant minority (30-40%) of patients benefit from very durable remissions after autoSCT, suggesting that some patients may be cured by this approach.[5,6] Conversely, approximately one third of patients relapse within 2 years of this intensive, potentially toxic treatment and therefore derive limited benefit. Toxicities include protracted fatigue, risk of infections and potentially secondary malignancies including secondary myelodysplastic syndrome and acute myeloid leukemia.[5-10] In current routine clinical practice, clinicians are unable to accurately predict which patients may benefit most from autoSCT. The results of some historical studies are now challenging to interpret for several reasons. Some studies were performed in the pre-rituximab era,[7,8] some included conditioning regimens now considered obsolete in FL (e.g., total body irradiation)[8,9] and others included a significant minority of patients receiving high-dose therapy as first-line therapy consolidation.[10,11] In general, published series report outcomes outlining standard clinical parameters, and there are few data with biological or functional imaging assessment of disease status prior to autoSCT in these published cohorts.

To date, there are no prospective data to guide therapeutic decision-making for patients with R/R FL in terms of discriminating which patients might benefit most from autoSCT. It is important that the benefits and curative potential of this potentially toxic therapeutic intervention are better understood in this setting.

Pooled analyses demonstrate the prognostic value of both baseline positron emission tomography (PET)-computed tomography (CT) and PET-based response assessment in FL. Total metabolic tumor volume[12] prior to front-line treatment was predictive of progression-free survival (PFS) in a large, pooled, prospective cohort of patients from the PRIMA, PET-Folliculaire and FOLL05 trials. Metabolic response after induction immunochemotherapy, graded according to a five-point scale (Deauville criteria),[13,14] also correlated strongly with PFS in a sub-analysis of separate large randomized clinical trials including PRIMA,[15] GALLIUM[16] and pooled data from three separate trials (PRIMA, PET-Folliculaire, and FOLL05).[17]

Compelling evidence from R/R Hodgkin lymphoma[18] and R/R diffuse large B-cell lymphoma[19,20] has shown response according to PET or other functional imaging status is a strong prognostic factor prior to autoSCT. For example, patients in the ORCHARRD trial[21] were scanned before autoSCT following three cycles of salvage immunochemotherapy: the PET-negative cohort had a superior PFS and overall survival (OS), with a 2-year PFS of 70% and 2-year OS of 78%, compared to the PET-positive cohort with a 2-year PFS of 32% and a 2-year OS of 43% (P=0.001 and P=0.0018, respectively).

Given the lack of evidence base for PET-CT-related prognostication in the pre-SCT setting in FL, but the clear prognostic value of PET-CT following front-line FL treatment, and compelling data from other lymphoma histologies, the clinical studies working group for the British Society of Blood and Marrow Transplantation and Cellular Therapy (BSBMTCT) conducted a retrospective registry analysis to study the outcomes of patients with R/R FL treated with autoSCT who had a preceding PET-CT response assessment. To our knowledge, this is the first series of patients with FL for whom outcomes following autoSCT according to PET-CT response pre-autoSCT is described. We therefore aimed to: (i) analyze outcomes of patients receiving an autoSCT for R/R FL in the modern era in the UK; (ii) analyze the outcomes according to the depth of PET-CT response prior to autoSCT; and (iii) analyze the therapeutic effect of autoSCT in deepening PET-based response.

Methods

We conducted a national, multicenter, retrospective BSBMTCT registry study to describe the characteristics and outcomes of patients ≥18 years of age with R/R FL who received an autoSCT at some point (first-line consolidation treatment or later lines) during their treatment pathway between 01/01/2015 and 31/12/2019. The study was reviewed and approved by the central institutional review board of the Clinical Studies Working Party of BSBMTCT prior to commencing (study reference: CTCR-1901). Relevant BSBMTCT-registered transplant centers (n=41) which were identified as having treated a FL patient with an autoSCT during the timeframe were contacted to obtain additional information regarding PET-CT responses. AutoSCT was defined according to the published European Blood and Marrow Transplantation Group (EBMT)/BSBMTCT criteria *(https://www.ebmt.org/sites/default/files/2018-03/MED-AB%20Forms%20Manual.pdf*). Status (complete metabolic response [CMR] and partial metabolic response at autoSCT) was defined according to the Lugano classification.[13] The occurrence of new sites of disease following a complete response (CR)/CMR lasting for ≥3 months was defined as a relapse, whereas it was considered progressive disease when CR/CMR had not been achieved. Post-transplant monitoring of patients for relapse/progressive disease was conducted according to the protocols of the local centers. OS was calculated by Kaplan-Meier analysis as the time from autoSCT to death from any cause. PFS was calculated by Kaplan-Meier analysis[22] as the time from autoSCT until FL relapse/progression or death from any cause. Non-relapse mortality was calculated by competing risks, including all causes of death occurring after autoSCT other than relapse, with relapse as the competing risk. Relapse rate was calculated

by competing risks as the time to relapse after autoSCT, with death without relapse as the competing risk. All four outcomes were censored at the date of last follow-up. Univariable and multivariable Cox regression analyses were used to examine the associations between baseline factors, PET status before autoSCT and PFS and OS.[23] The proportional hazard assumption was tested by Schoenfeld residuals for all models. Fine-Grey competing risk analysis was used for equivalent associations with relapse risk and non-relapse mortality. Multivariable analyses were performed by backward selection from candidate factors with $P<0.2$ in univariate analysis and of clinical relevance. The Deauville score was excluded from multivariable analysis because it was structurally correlated with PET status and because data were incomplete. Likewise, status at transplant was structurally correlated with PET status. Logistic regression (for continuous variables), Wilcoxon rank sum (for ordered categorical variables) or Fisher exact (for binary variables) tests were used to compare PET remission status between different baseline groups. Statistical analyses were performed in Stata 17.0 (StataCorp, College Station, TX, USA). *P* values <0.05 were regarding as statistically significant.

The primary endpoint of the study was PFS and was stratified according to PET-based response prior to autoSCT. Key secondary endpoints included OS, non-relapse mortality, cumulative incidence of relapse, engraftment and change in the depth of PET status after autoSCT. Patients' characteristics collected included age, gender, comorbidity index, Karnofsky performance status at autoSCT, prior anti-CD20 monoclonal antibody exposure, duration of first remission (including POD24 status), prior lines of therapy, and salvage regimen(s) used before autoSCT. FL characteristics collected included components of the FL International Prognostic Index (FLIPI) at relapse (age, stage, raised serum lactate dehydrogenase, hemoglobin, number of nodal areas involved), and prior high-grade transformation (whether present at initial diagnosis or relapse). PET-CT remission or not (mandatory) and ordinal Deauville score (on a scale from 1 to 5) if reported (not mandatory but recommended) were documented before and after (approximately day 100) autoSCT. All scans were acquired after publication of the Lugano classification which recommended the use of the Deauville score to assess CMR (scores 1-3) *versus* non-CMR (scores 4 and 5) and was widely adopted in the UK. CT-based responses were reported as per the CT-based assessment of the Lugano classification. The timing of scans during re-induction treatment was not standardized and was determined by the local investigators. Scans were not re-reviewed for this analysis. The autoSCT conditioning regimen and source of hematopoietic stem cells were also collected. Follow-up was censored at the most recent hospital visit or death. Patients without an assessment of PET status at time of transplant and those with biopsy-proven high-grade transformation (include grade 3B FL) at the relapse that immediately preceded the autoSCT were excluded from the analysis. During the dates the study recruited, in the UK there was no commissioning for any routine consolidation therapy in patients undergoing autoSCT for FL and accordingly consolidation therapy was not administered. The database was locked in March 2021 for analysis.

Results

A total of 381 cases of FL treated with autoSCT were identified within the BSBMTCT registry across 41 centers. Thirty centers responded reporting a total of 172 cases with available data for the final analysis. One-hundred and twenty-seven cases were excluded due to lack of PET data or due to transformed disease at the time of the preceding relapse before autoSCT (Consort *Online Supplementary Figure S1*). Patients excluded due to lack of PET data were similar to those included, but overall were less heavily pre-treated and had lower FLIPI scores (see *Online Supplementary Table S1* for further details).

The median age of the total cohort was 51 years (range, 17-69) at FL diagnosis and the median age at the time of autoSCT was 55 years (range, 22-74). The median time from FL diagnosis to autoSCT was 4 years and 2 months (range, 3 months to 26 years). Fifty-six percent (97/172) of patients were male. Most patients underwent conditioning with BEAM (carmustine, etoposide, cytarabine and melphalan) (48%) or LEAM (lomustine, etoposide, cytarabine and melphalan) (34%). The median number of prior lines of treatment for all patients before autoSCT was three (range, 1-6), and only 2% of patients underwent SCT after first-line therapy. Prior histological transformation was documented in 22 (13%) patients. The median Karnofsky performance status at autoSCT was 90 (range, 70-100). Sixty-three percent of patients had a Hematopoietic Cell Transplantation Comorbidity Index (HCT-CI) of 0, the median HCT-CI was 0 (range, 0-6). Patient- and treatment-related details according to PET status at autoSCT are summarized in Table 1.

PET status at the time of transplant was reported as non-CMR in 57 patients (33%) and CMR in 115 (67%). The ordinal Deauville score was reported for 82 patients (47%) and was missing for 90 patients (53%). Among the 82 cases in which the Deauville score was provided, it was 1-3 in 57 patients (69.5%), 4 in 23 patients (28%), and 5 in two patients (2%). Seventy-five patients had a PET status recorded at follow-up. Of 33/75 patients who were classified as non-CMR before autoSCT and had a post-autoSCT status recorded, 21 (64%) obtained a CMR after the autoSCT. Of the 103 patients in CMR for whom the most

Table 1. Patient and disease characteristics according to positron emission tomography status at transplant.

		CMR at SCT N=115	Non-CMR at SCT N=57	All patients N=172	*P* value Non-CMR *vs.* CMR[a]
Age at diagnosis, years	Median (range)	54 (30-69)	51 (17-69)	53 (17-69)	0.1587[a]
Age at transplant, years	Median (range) > 60 years, N (%)	60 (35-73) 59 (51%)	55 (22-74) 21 (37%)	58 (22-74) 80 (47%)	0.1224[a] 0.077[b]
Time from diagnosis to SCT	Median (range)	4y 2m (4m-26y)	3y 9m (4m-21y)	4y 2m (4m-26y)	0.5003[a]
Sex	Male, N (%)	62 (54)	35 (61)	97 (56)	0.415[b]
Number of lines of prior treatment	1, N (%) 2, N (%) 3, N (%) 4+, N (%) Median (range)	2 (2) 48 (42) 40 (35) 25 (22) 3 (1-6)	1 (2) 15 (27) 17 (30) 23 (41) 3 (1-6)	3 (2) 63 (37) 57 (33) 48 (28) 3 (1-6)	0.089[c]
Prior rituximab	Yes, N (%)	85 (74)	48 (84)	133 (77)	0.175[b]
Prior obinutuzumab	Yes, N (%)	13 (11)	7 (12)	20 (12)	1.000[b]
POD24	Yes, N (%) Unknown, N	24 (48) 65	9 (39) 34	33 (45) 99	0.614[b]
Karnofsky status at SCT	100, N (%) 90, N (%) 80, N (%) 70, N (%) Unknown, N	30 (27) 65 (59) 15 (14) 0 (0) 5	15 (28) 36 (67) 2 (4) 1 (2) 3	45 (27) 101 (62) 17 (10) 1 (1) 8	0.468[c]
Comorbidities: HCT-CI	0, N (%) 1, N (%) 2, N (%) 3+, N (%) Median (range)	77 (67) 21 (18) 6 (5) 11 (10) 0 (0-6)	31 (54) 11 (19) 5 (9) 10 (19) 0 (0-6)	108 (63) 32 (19) 11 (6) 21 (12) 0 (0-6)	0.072[c]
Conditioning[d]	BEAM, N (%) LEAM, N (%) Others, N (%)	52 (46) 44 (39) 18 (17)	30 (53) 14 (25) 12 (23)	82 (48) 58 (34) 31 (18)	0.246[b] 0.418[b] (BEAM *vs.* others)
HGT before SCT		17 (15)	5 (9)	22 (13)	0.337[b]
Histological grading	1, N (%) 2, N (%) 3, N (%) Unknown, N	24 (28) 30 (35) 31 (36) 30	11 (24) 26 (58) 8 (18) 12	35 (27) 56 (43) 39 (30) 42	0.030[b] 0.279[c]
Time since last relapse, m[e]	Median (range)	8 (1-54)	7 (1-24)	8 (1-54)	0.459[a]
Ann Arbor stage	I-II, N (%) III-IV, N (%) Unknown, N	14 (21) 54 (79) 47	4 (11) 34 (89) 19	18 (17) 88 (83) 70	0.604[c]
Number of nodal sites	0-4, N (%) Unknown, N	43 (74) 57	23 (68) 23	66 (72) 80	0.632[b]
LDH	>ULN, N (%) Unknown, N	12 (27) 70	7 (26) 30	19 (26) 100	1.000[b]
Hemoglobin, g/L	Median (range) Unknown, N	125.5 (80-163) 63	130 (51-162) 24	127 (51-163)	0.797[a]
Deauville score	1, N (%) 2, N (%) 3, N (%) 4, N (%) 5, N (%) Unknown	17 (30) 24 (42) 16 (28) 0 0 58	0 0 0 23 (92) 2 (8) 32	17 (21) 24 (29) 16 (20) 23 (28) 2 (2) 90	N/A
Status at transplant	CR, N (%) PR, N (%) SD / relapse / PD, N (%)	99 (86) 15 (13) 1 (1)	6 (11) 47 (87) 1 (2)	105 (62) 62 (37) 2 (1)	**0.0005**[b]
FLIPI category	Low, N (%) Low-intermediate, N (%) High intermediate, N (%) High, N (%)	63 (55) 28 (24) 22 (18) 2 (2)	23 (40) 19 (33) 11 (19) 4 (7)	86 (50) 47 (27) 33 (19) 6 (3)	**0.085**[c]

[a]Wilcoxon rank-sum test. [b]Fisher exact test. [c]Logistic regression. [d]Conditioning unknown in one patient. [e]Does not apply to patients in first complete remission or with refractory disease. CMR: complete metabolic remission; SCT: stem cell transplantation; m: months; y: years; POD24: progression of disease within 24 months; HCT-CI: Hematopoietic Cell Transplantation Comorbidity Index; BEAM: carmustine, etoposide, cytarabine, melphalan; LEAM: lomustine, etoposide, cytarabine, melphalan; HGT: high-grade transformation; LDH: lactate dehydrogenase; ULN: upper limit of normal; na: not available; CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; FLIPI: Follicular Lymphoma International Prognostic Index.

recent prior regimen was known, 92% (n=95) received rituximab, most commonly alongside cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP, n=46) or bendamustine (R-bendamustine, n=20). These were also the most common prior regimens in patients not obtaining CMR before autoSCT (R-CHOP and R-bendamustine, both n=14 in 43 rituximab-exposed patients). Further details are provided in *Online Supplementary Table S2*.

There was no association between age at autoSCT, sex, number of months since last relapse, Karnofsky performance status or HCT-CI, and achieving CMR before autoSCT. There were indications of a tendency for patients who achieved CMR before autoSCT to have had fewer lines of therapy (P=0.089) and have a lower FLIPI score at the time of the relapse before autoSCT (P=0.085) but these factors did not reach statistical significance. Histological grade at relapse (grade 3a *vs.* 1-2) (P=0.030) was associated with not having a CMR prior to autoSCT.

Of those with available data regarding POD24, 45% (33/73) of patients had experienced POD24 after first-line therapy; POD24 was not associated with pre-autoSCT PET status.

The median follow-up following autoSCT was 27 months (range, 3–70 months). The median PFS for the whole cohort after autoSCT was 28 months (interquartile range [IQR], 23-36), (*Online Supplementary Figure S2A*), the median time to relapse was 50 months (IQR, 16 months – not reached) and the median OS was 57 months (IQR, 42 months – not reached) (*Online Supplementary Figure S2B*). Overall, the day-100 and 1-year non-relapse mortality was 5% and 6%, respectively. There were 14 deaths in remission. These included deaths caused by early infection (n=8, all before day 100), late infection (n=2, both after allogeneic SCT), secondary malignancy (n=2, acute myeloid leukemia, and unknown) and unknown causes (n=2) (*Online Supplementary Table S3*).

Survival analysis, engraftment and secondary malignancies are presented in Table 2. There were five secondary malignancies in four patients (2%) in the FL cohort, all of which were in the CMR group. These were melanoma (n=1), myelodysplastic syndrome (n=1), myelodysplastic syndrome and vulval cancer (n=1) and acute myeloid leukemia (n=1). Engraftment after autoSCT was not associated with PET status before the transplant. PET status at the time of transplant was strongly predictive of PFS; 115 patients

Table 2. Survival outcomes, engraftment and secondary malignancies.

		CMR at SCT N=115	Non-CMR at SCT N=57	All patients N=172	*P* value Non-CMR *vs.* CMR[a]
Follow-up	Median (range)	2y+4m (3m+5y-7m)	2y+3m (8m+5y-10m)	2y+3m (3m+5y-10m)	0.733
Neutrophil recovery	Yes, N	109	55	164	
	Never fell, N	1	0	1	
	No (all died before recovery), N	3	1	4	
	Unknown, N	2	1	3	
Recovery time, days	Median (range)	11 (8-23)	11 (6-28)	11 (6-28)	0.614
Platelet recovery	Yes, N	86	47	133	
	Never below, N	2	0	2	
	No (all died before recovery), N	6	3	9	
	Unknown (after discharge), N	21	7	28	
Recovery time, days	Median (range)	18 (7-198)	19 (8-46)	18 (7-198)	0.833
Status at follow-up	Alive, N	95	43	138	See outcomes in Table 3
	In CR/PR, N	70	24	94	
	After relapse/progression, N	25	19	44	
	Dead, N	20	14	34	
	After relapse[b], N	13	7	20	
	In remission, N	7	7	14	
Secondary malignancies	Yes, N	4	0	4	0.303[c]
PET at follow up (survivors only)	Negative, N (%)	32 (73)	17 (59)	49 (67)	0.309[c]
	Positive, N (%)	12 (27)	12 (41)	24 (33)	
	Unknown, N	51	14	65	

[a]Cox model unless otherwise specified. [b]Four patients (3 CMR and 1 non-CMR) had non-relapse causes listed for death, although they had relapsed (1 graft-*versus*-host disease, 1 Gram-negative sepsis, 1 acute respiratory distress syndrome and 1 renal failure). [c]Fisher exact test; CMR: complete metabolic remission; SCT: stem cell transplantation; CR: complete response; PR: partial response; PET: positron emission tomography.

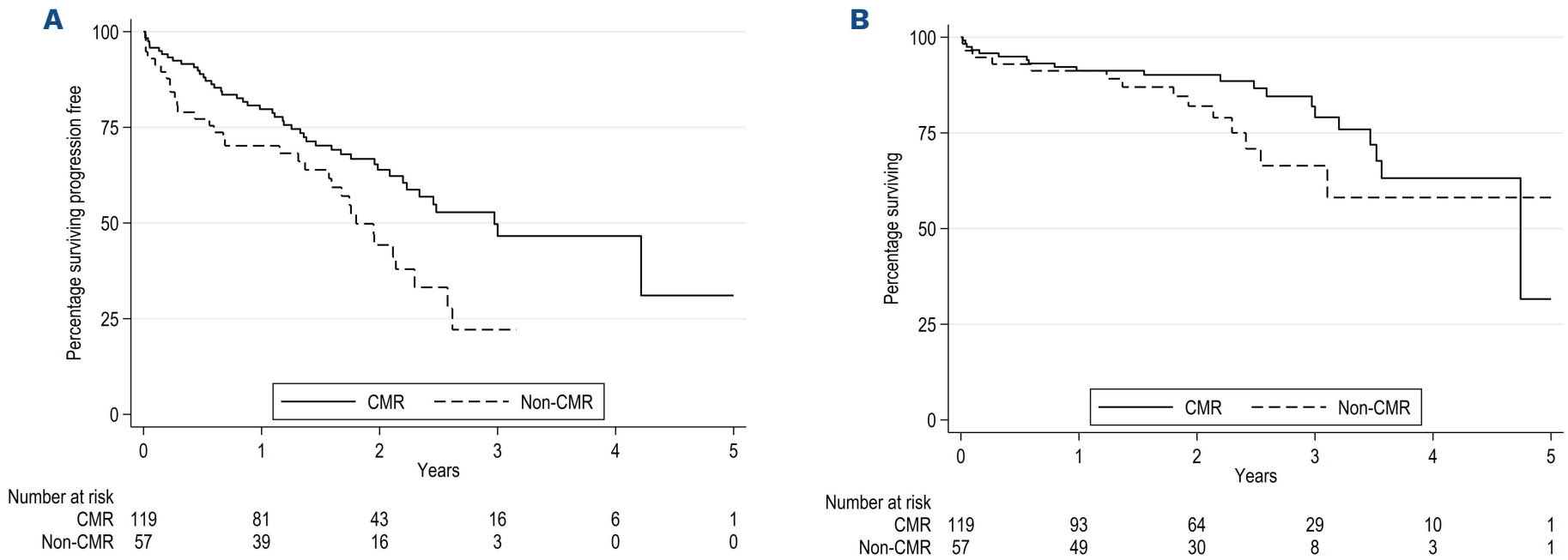

Figure 1. Survival according to positron emission tomography status before autologous stem cell transplantation. (A) Progression-free survival and (B) overall survival according to positron emission tomography status before autologous stem cell transplantation. CMR: complete metabolic remission.

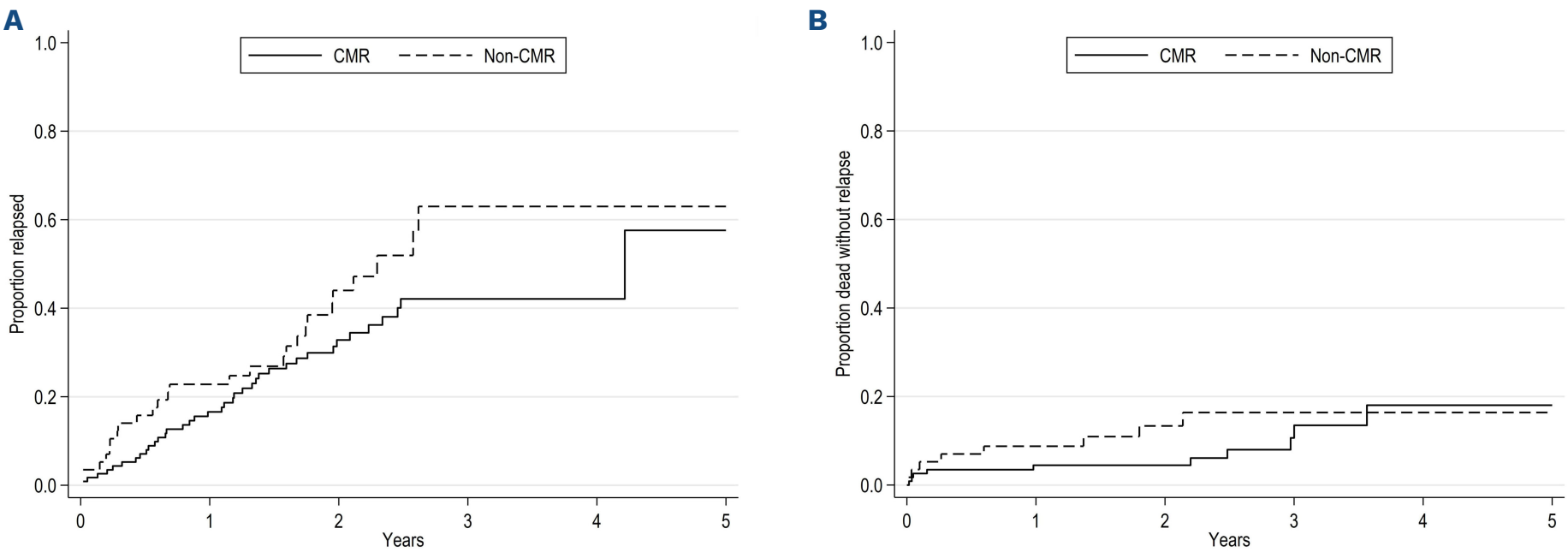

Figure 2. Relapse and non-relapse mortality according to positron emission tomography status before autologous stem cell transplantation. (A) Relapse rate and (B) non-relapse mortality according to positron emission tomography status before autologous stem cell transplantation. CMR: complete metabolic remission.

with a CMR had a median PFS of 36 months (IQR, 15 months –not reached) *versus* 22 months (IQR, 7 – 31 months) for the 57 with non-CMR prior to transplant, hazard ratio (HR)=1.80 (95% confidence interval [95% CI]: 1.15-2.84), *P*=0.011). The 2-year PFS was 64% *versus* 44% and the 3-year PFS was 50% *versus* 22% for CMR and non-CMR patients, respectively (Figure 1A, Table 2). Non-CMR was associated with a trend to increased relapse rate (HR=1.51, 95% CI: 0.92-2.47; *P*=0.101) (Figure 2A). Non-CMR was also associated with a trend towards reduced OS, but this did not reach statistical significance (HR=1.74, 95% CI: 0.87-3.49; *P*=0.116) (Figure 1B). Non-relapse mortality was not associated with PET status before autoSCT (HR=1.79, *P*=0.211) (Figure 2B).

Factors associated with improved PFS by univariate analysis (Table 3) were age ≤60 years (age >60 years: HR=1.61, 95% CI: 1.03-2.51; *P*=0.038) and CMR before autoSCT (non-CMR: HR=1.80, 95% CI: 1.15-2.84; *P*=0.011) and ordinal Deauville score (continuous variable, HR=1.32, 95% CI: 1.00-1.75; *P*=0.049) (*Online Supplementary Figure S3A*). Age and PET status (CMR *vs.* non-CMR) remained strongly statistically significant for PFS by multivariable analysis (non-CMR: HR=2.02, 95% CI: 1.27-3.21; *P*=0.003; age >60 years: HR=1.81, *P*=0.011) (Table 4). Risk factors associated with improved OS that were significant by multivariate analysis were fewer prior lines of therapy (HR=0.59, 95% CI: 0.38-0.90; *P*=0.015), lower Karnofsky status (continuous variable HR=0.94, 95% CI: 0.89-0.99; *P*=0.047) and risk factors associated with worse OS were remission status at transplant (non-CMR: HR=3.08, 95% CI: 1.31-7.24; *P*=0.010)

Table 3. Univariable analyses.

			OS		PFS		RR[a]		NRM[b]	
	Levels	N	% at 3 years (95% CI)	HR (95% CI)	% at 3 years (95% CI)	HR (95% CI)	% at 3 years (95% CI)	HR (95% CI)	% at 3 years (95% CI)	HR (95% CI)
Age, years	≤60	92	81 (67-90)	2.26	50 (35-63)	1.61	41 (28-54)	1.53	10 (4-19)	1.69
	>60	80	73 (58-83)	(1.10-4.65)	31 (18-45)	(1.03-2.51)	57 (42-70)	(0.94-2.49)	15 (7-27)	(0.66-4.41)
	Continuous			1.65		1.21		1.17		1.22
	per 10 years			(1.03-2.66)		(0.91 – 1.60)		(0.83-1.64)		(0.65-2.28)
Sex	Male	97	73 (59-83)	0.66	35 (22-48)	0.82	53 (40-65)	0.82	16 (8-27)	0.62
	Female	75	83 (68-91)	(0.32-1.33)	49 (33-63)	(0.52-1.29)	42 (28-56)	(0.49-1.35)	9 (3-18)	(0.23-1.67)
Lines of	Continuous			0.78		1.09		1.14		0.83
prior treatment				(0.55-1.11)		(0.88-1.36)		(0.90-1.43		(0.52-1.34)
Prior rituximab	No	39	66 (43-82)	0.52	42 (23-61)	0.78	45 (27-61)	0.76	23 (8-41)	0.55
	Yes	133	80 (69-88)	(0.25-1.07)	41 (29-52)	(0.46-1.31)	49 (38-60)	(0.43-1.34)	10 (5-18)	(0.21-1.45)
Prior	No	152	77 (67-84)	0.83	41 (30-51)	1.13	48 (38-58)	1.14	13 (7-21)	0.64
obinutuzumab	Yes	20	79 (32-95)	(0.20-3.53)	47 (17-72)	(0.52-2.49)	48 (18-73)	(0.50-2.58)	5 (1-21)	(0.08-4.95)
Karnofsky	Continuous			0.65		0.96		1.20		0.58
status at SCT	per 10 units			(0.35-1.20)		(0.65-1.42)		(0.75-1.90)		(0.27-1.24)
Comorbidities	None	96	77 (64-86)	1.09	47 (34-58)	1.19	46 (33-57)	0.99	12 (6-21)	1.38
	Yes	74	77 (60-88)	(0.55-2.14)	31 (16-48)	(0.76-1.87)	54 (36-68)	(0.61-1.63)	14 (5-27)	(0.55-3.48)
HCT-CI	Continuous			0.96		0.99		0.97		1.01
				(0.72-1.27)		(0.83-1.18)		(0.80-1.17)		(0.74-1.36)
Conditioning	BEAM	90	75 (57-86)	1.18	46 (29-61)	1.29	43 (29-56)	1.31	15 (6-29)	1.00
	Other	82	78 (66-87)	(0.60-2.34)	35 (23-48)	(0.83-2.02)	54 (40-67)	(0.80-2.13)	11 (5-20)	(0.39-2.53)
Days since last	Continuous			1.00		1.00		1.00		0.99
relapse				(0.99-1.01)		(0.99-1.00)		(0.99-1.01)		(0.98-1.01)
Nodal sites	0-4	66	82 (66-90)	2.32	43 (28-56)	1.21	51 (36-64)	0.75	7 (2-17)	**4.12**
	>4	26	65 (42-81)	(1.00-5.38)	40 (20-59)	(0.66-2.23)	39 (19-58)	(0.37-1.52)	21 (8-39)	**(1.25-13.7)**
	Continuous			1.17		1.02		0.94		**1.28**
				(0.96-1.42)		(0.89-1.18)		(0.81-1.10)		**(1.02-1.60)**
Ann Arbor stage	1-2	18	88 (39-98)	2.00	55 (23-79)	1.53	45 (16-70)	1.36	0	1.80
	3-4	88	76 (64-85)	(0.47-8.54)	38 (26-49)	(0.69-3.40)	52 (39-63)	(0.59-3.15	12 (6-21)	(0.25-13.1)
	Continuous			1.36		1.22		1.12		1.40
				(0.75-2.44)		(0.86-1.73)		(0.78-1.59)		(0.61-3.21)
Histological	1-2	91	82 (70-89)	1.62	38 (25-51)	0.83	56 (42-68)	0.67	9 (4-16)	1.52
grade	3	39	64 (40-81)	(0.72-3.66)	53 (32-70)	(0.46-1.49)	33 (17-51)	(0.33-1.33)	18 (6-36)	(0.50-4.64)
	Continuous			1.36		0.94		0.88		1.31
				(0.81-2.27)		(0.68-1.31)		(0.62-1.24)		(0.64-2.71)

Continued on following page.

			OS		PFS		RR[a]		NRM[b]	
	Levels	N	% at 3 years (95% CI)	HR (95% CI)	% at 3 years (95% CI)	HR (95% CI)	% at 3 years (95% CI)	HR (95% CI)	% at 3 years (95% CI)	HR (95% CI)
POD24	No	40	74 (53-86)	1.60	49 (29-66)	1.32	36 (19-53)	1.42	18 (6-33)	0.54
	Yes	33	71 (46-86)	(0.74-3.45)	36 (18-55)	(0.77-2.26)	54 (33-71)	(0.76-2.67)	10 (3-24)	(0.11-2.63)
LDH	Normal	53	74 (55-86)	0.98	38 (21-54)	1.18	52 (34-68)	1.09	9 (3-21)	1.70
	>ULN	19	82 (53-94)	(0.33-2.91)	40 (18-61)	(0.60-2.32)	49 (25-70)	(0.52-2.31)	11 (2-29)	(0.40-7.14)
Hemoglobin,	<120	31	75 (52-88)	0.78	38 (19-57)	0.78	57 (35-74)	1.89	4 (0-19)	4.82
g/L	≥120	54	82 (66-91)	(0.30-2.03)	46 (30-61)	(0.42-1.46)	41 (25-56)	(0.97-3.68)	13 (5-25)	(0.62-37.5)
	Continuous			0.90		0.98		0.93		1.02
	per 10g/L			(0.74-1.10)		(0.85-1.12)		(0.80-1.07)		(0.99-1.04)
CT status at SCT	CR	105	85 (73-92)	**2.35**	50 (37-62)	**1.77**	47 (34-59)	1.16	6 (2-14)	**3.41**
	PR/SD/PD	67	65 (48-78)	**(1.19-4.65)**	26 (12-42)	**(1.13-2.77)**	52 (36-66)	(0.71-1.89)	23 (12-37)	**(1.31-8.89)**
Deauville score	Continuous			**1.65**		**1.32**		1.08		**1.76**
				(1.07-2.53)		**(1.00-1.75)**		(0.80-1.44)		**(1.04-2.98)**
FLIPI	Continuous			1.34		1.15		1.04		1.50
				(0.96-1.87)		(0.94-1.41)		(0.85-1.28)		(0.87-2.57)
FLIPI category	Continuous			1.20		1.10		1.05		1.30
low / low int. /				(0.92-1.57)		(0.94-1.30)		(0.88-1.24)		(0.84-2.01)
high int. / high										
PET status at SCT	CMR	115	82 (71-90)	1.74	50 (37-61)	**1.80**	42 (31-53)	1.51	11 (4-20)	1.79
	Non-CMR	57	66 (47-80)	(0.87-3.49)	22 (9-40)	**(1.15-2.84)**	63 (43-78)	(0.92-2.47)	16 (7-28)	(0.72-4.45)

[a]By competing risks regression, death without relapse/progression being the competing risk. [b]By competing risks regression, death from relapse being the competing risk. OS: overall survival; PFS: progression-free survival; RR: relapse rate; NRM: non-relapse mortality; 95% CI: 95% confidence interval; HR: hazard ratio; SCT: stem cell transplantation; HCT-CI: Hematopoietic Cell Transplantation Comorbidity Index; BEAM: carmustine, etoposide, cytarabine, melphalan; POD24: progression of disease within 24 months; ULN: upper limit of normal; CT: computed tomography; PR: partial response; SD: stable disease; PD: progressive disease; FLIPI: Follicular Lymphoma International Prognostic Index; PET: positron emission tomography; CMR: complete metabolic remission.

(*Online Supplementary Figure S3B*) and age >60 years (HR=3.76, 95% CI: 1.59-8.90; *P*=0.003). PET status and age were the only two factors independently associated with increased risk of relapse after autoSCT by multivariable analysis (non-CMR: HR=1.64, 95% CI: 1.01-2.65; *P*=0.046). POD24 status was not associated with any of these specific survival or relapse outcome measures. PET status was not independently associated with a difference in non-relapse mortality.

Table 4. Multivariable analysis.

Overall survival (N=163 patients, 28 events)			
Factor	HR	95% CI	*P* value
Age over 60 years	3.76	1.59-8.90	0.003
Number of prior lines	0.59	0.38-0.90	0.015
Karnofsky status at SCT	0.94	0.89-0.99	0.047
PET status at SCT: non-CMR	3.08	1.31-7.24	0.010
Progression free survival (N=172 patients, 78 events)			
Factor	HR	95% CI	*P* value
Age over 60 years	1.81	1.15-2.85	0.011
PET status at SCT: non-CMR	2.02	1.27-3.21	0.003
Relapse rate (N=172 patients, 64 events)			
Factor	HR	95% CI	*P* value
Age over 60 years	1.64	1.02-2.66	0.043
PET status at SCT: non-CMR	1.64	1.01-2.65	0.046
Non-relapse mortality rate (N=92 patients, 11 events)			
Factor	HR	95% CI	*P* value
>4 nodal sites	2.65	0.87-8.13	0.088
PET status at SCT: non-CMR	1.71	0.63-4.67	0.293

Candidate factors excluded for overall survival: time since last relapse (*P*=0.69), FLIPI (*P*=0.42), >4 nodal sites (*P*=0.25), prior rituximab (*P*=0.14). *P* for entry=0.05, *P* for removal=0.10. Candidate factor excluded for progression-free survival: FLIPI (*P*=0.60), *P* for entry=0.05, *P* for removal=0.10. Candidate factor excluded for relapse rate: hemoglobin <120 g/L (*P*=0.25), *P* for entry=0.025; *P* for removal=0.10. Candidate factors excluded for non-relapse mortality: FLIPI (*P*=0.45), hemoglobin <120 g/L (*P*=0.13), age over 60 years old (*P*=0.10), Karnofsky status at transplant (*P*=0.15). FLIPI: Follicular Lymphoma International Prognostic Index; SCT: stem cell transplantation; PET: positron emission tomography; CMR: complete metabolic remission.

Discussion

To the authors' knowledge, this BSBMTCT series represents the first and largest experience outlining the value of PET-CT prior to autoSCT in patients with R/R FL. Whereas PET status prior to autoSCT has been previously reported to be predictive of PFS in relapsed classical Hodgkin lymphoma and diffuse large B-cell lymphoma, there have been no studies investigating the impact of PET status on outcome for R/R FL patients undergoing autoSCT. The results of this study demonstrate for the first time that patients with FL who achieve a PET-negative remission (CMR *vs.* non-CMR) prior to consolidation autoSCT have significantly improved PFS compared to those patients who fail to achieve CMR (HR=1.80, 95% CI: 1.15-2.84; *P*=0.011). There was a non-significant trend in relapse rate for those undergoing autoSCT in CMR and there was a non-significant trend towards improved OS in those who achieved CMR. Factors that were significant for improved PFS in multivariate analysis were age ≤60 years, and CMR at the time of transplantation and risk factors for OS that retained significance in multivariate analysis were age ≤60 years, and CMR at time of transplantation, number of lines of prior treatment, and Karnofsky score. For patients with data available on POD24 status, we observed no association with worse PFS or OS after autoSCT. Although our study lacked data on this variable in a large proportion of cases, this finding corroborates others indicating that autoSCT has a role in the management of patients with POD24 but chemo-sensitive relapse following early failure of front-line treatment.[4] We cannot however exclude the possibility of selection and immortality bias, as the analysis included only patients who experienced POD24 and received an autoSCT and further prospective studies are needed to identify optimal approaches for patients with early treatment failure.

Given that autoSCT carries a risk of non-relapse mortality, significant morbidity, prolonged in-patient admission, a not insignificant risk of secondary hematologic malignancy (a recent BSBMT report of all lymphoma types reported a rate of 3% in over 1,000 patients given BEAM/LEAM and autoSCT[24]) and incurs significant cost, it is important that the ability to predict patients who may be expected to have long remissions with this intensive treatment are improved. Similarly, it is also important that we develop tools to predict which patients may be anticipated to have short-lived benefit from this intensive therapy so that alternative treatment modalities can be assessed in this group and avoid exposing patients to this potentially toxic treatment.

Here we present a first step in risk-stratifying patients with R/R FL for autoSCT. Patients in CMR prior to transplant had a 50% (95% CI: 37-61%) chance of remaining alive and progression free at 3 years whereas those who failed to obtain a CMR at this time-point had only a 22% (95% CI: 9-40%) chance of being alive and free of progression at 3 years. Previous retrospective series have identified possible plateaus in the survival curves of patients with FL who have undergone autoSCT and long-term follow-up of this study will be performed to establish whether this is observed and whether PET status remains predictive of longer-term remission.

These data support the ongoing role of autoSCT in consolidating remissions in patients with R/R FL. The median PFS of 28 months and 3-year PFS rate of 40% (95% CI: 30-50) observed in this study for the whole cohort compares favorably with those of other series[3-5,11] and if this intervention can be further refined so that it is directed towards those most likely to benefit, the outcomes for patients undergoing this procedure may be further improved.

This is an era of unprecedented development of new therapeutic agents and strategies in R/R FL. While direct comparisons between outcomes of autoSCT and some of these novel approaches are challenging in the absence of randomized controlled trials, it is pertinent to consider how the outcomes for patients undergoing autoSCT for R/R FL compare to those undergoing such novel approaches. The use of allogeneic SCT has been reported in relapsed FL and one series reported a 4-year PFS of 76% but with a non-relapse mortality of 15% and thus the outcomes for PET-negative patients in this study with a 4-year PFS of 64% (46-78%) may be considered comparable.[25] The immunomodulatory drug lenalidomide in combination with rituximab was used in relapsed FL in the AUGMENT trial, giving an impressive median PFS of 39.4 months although it should be noted that the median number of prior lines of therapy in the AUGMENT trial was only one with a substantial number of patients having received no prior chemotherapy, so it is hard to compare with the cohort of patients in this study who had received a median of three lines.[26] A number of PI3 kinase inhibitors have been licensed by the Food and Drug Administration in the USA and show modest response rates, low CR rates and relatively short median PFS of 9-11 months in heavily pre-treated FL.[27,28] Antibody-drug conjugates such as the CD19 targeting agent loncastuximab tesirine (ADCT-402) are showing promise; ADCT-402 produced a high CR rate in 15 R/R FL patients (CR 53%) but the follow-up to date is short.[29] The oral EZH2 inhibitor tazemetostat has yielded high remission rates with a median PFS of 13.8 months in patients with *EZH2* mutations.[30] There is great interest in the development of CD3-CD20 bispecific antibodies in B-cell non-Hodgkin lymphoma and high remission rates in R/R FL have been reported with mosunetuzumab[31] (overall response rate 67%, CR 51%, median duration of response 20.4 months) and glofitamab[32] (overall response rate 69%, CR 59%, median PFS 11.8 months) but follow-up is not sufficient to understand how durable remissions with these agents will be in patients with R/R FL. The place of autoSCT in the management of R/R FL also needs to be considered in light of the development of anti-CD19 directed chimeric antigen receptor T-cell therapy. Two prospective phase II trials (ZUMA-5 assessing axicabtagene ciloleucel, n=108, ELARA assessing tisagenlecleucel, n=97) documented high overall response and CR rates (ZUMA-5 overall response rate 92%, CR 80%; ELARA overall response rate 86.2%, CR 66%) in heavily pre-treated R/R FL patients.[33,34] Although chimeric antigen receptor T-cell therapy and bispecific antibodies are particularly promising therapies in R/R FL, the reported median follow-up across all these studies (e.g. ELARA, median 10.9 months, ZUMA-5, median 17 months) is relatively short and the curative potential of these approaches remains uncertain. Thus, although there are many new treatment options in development for R/R FL, there are few that have yet been demonstrated to produce remissions as durable as those achieved by autoSCT in the historical literature and in patients in this study who achieved CMR to autoSCT.

There are limitations to this retrospective registry study, most notably the PET scans were not centrally reviewed for this study and some data points were not available for all patients, especially the Deauville score, FLIPI score, and POD24 status. Additionally, we cannot exclude a theoretical selection bias in that the study only collected data on patients who underwent autoSCT and therefore data were not captured on patients who may have been intended to undergo autoSCT but did not receive this treatment for example due to inadequate response to re-induction therapy. We also acknowledge that relatively little is known regarding the relative proportion of patients with R/R FL who receive an autoSCT compared to other therapies in 2022, and recognize that this will vary globally[1] according to national guidance, clinical trial options and the availability of novel therapeutics including bispecific antibodies and chimeric antigen receptor T-cell therapy.

We believe these intriguing data support the rationale for further efforts to define which patients with FL should undergo autoSCT. A prospective evaluation of the impact of PET remission status on transplant outcome would help to define this role. As we continue to gain better understanding of the molecular pathogenesis and evolution of FL, it may also be possible to define biomarkers, in conjunction with PET, which aid in accurately predicting who stands to benefit most from autoSCT and who should be considered for alternative novel treatment strategies. Such research would be timely as we aim to integrate the plethora of new therapeutic strategies into the treatment paradigm for patients with relapsed FL.

Disclosures

No conflicts of interest to disclose.

Contributions

WT and TAE contributed equally to writing the paper, data collection and analysis, as well as the study design and conception; all other authors contributed to the data collection. SB and JO contributed to writing the paper and the analysis. RMP, CA, RM, and JL contributed to the analysis and data collection. BC, CC, AB, MG, EN and KO contributed

to the data collection. All authors reviewed the manuscript and approved its submission.

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Data-sharing statement

Please email toby.eyre@ouh.nhs.uk for requests.

References

1. Link BK, Day B, Zhou X, et al. Second-line and subsequent therapy and outcomes for follicular lymphoma in the United States: data from the observational national LymphoCare study. Br J Haematol. 2019;184(4):660-663.
2. McNamara C, Montoto S, Eyre TA, et al. The investigation and management of follicular lymphoma. Br J Haematol. 2020;191(3):363-381.
3. Casulo C, Friedberg JW, Ahn KW, et al. Autologous transplantation in follicular lymphoma with early therapy failure: a national LymphoCare study and Center for International Blood and Marrow Transplant Research analysis. Biol. Blood Marrow Transplant. 2018;24(6):1163-1171.
4. Smith SM, Godfrey J, Ahn KW, et al. Autologous transplantation versus allogeneic transplantation in patients with follicular lymphoma experiencing early treatment failure. Cancer. 2018;124(12):2541-2551.
5. Robinson SP, Canals C, Luang JJ, et al. The outcome of reduced intensity allogeneic stem cell transplantation and autologous stem cell transplantation when performed as a first transplant strategy in relapsed follicular lymphoma: an analysis from the Lymphoma Working Party of the EBMT. Bone Marrow Transplant. 2013;48(11):1409-1414.
6. Vose JM, Bierman PJ, Loberiza FR, et al. Long-term outcomes of autologous stem cell transplantation for follicular non-Hodgkin lymphoma: effect of histological grade and Follicular International Prognostic Index. Biol Blood Marrow Transplant. 2008;14(1):36-42.
7. Montoto S, Canals C, Rohatiner AZS, et al. Long-term follow-up of high-dose treatment with autologous haematopoietic progenitor cell support in 693 patients with follicular lymphoma: an EBMT registry study. Leukemia. 2007;21(11):2324-2331.
8. Rohatiner AZS, Nadler L, Davies AJ, et al. Myeloablative therapy with autologous bone marrow transplantation for follicular lymphoma at the time of second or subsequent remission: long-term follow-up. J Clin Oncol. 2007;25(18):2554-2559.
9. Evens AM, Vanderplas A, Lacasce AS, et al. Stem cell transplantation for follicular lymphoma relapsed/refractory after prior rituximab: a comprehensive analysis from the NCCN lymphoma outcomes project. Cancer. 2013;119(20):3662-3671.
10. Jiménez-Ubieto A, Grande C, Caballero D, et al. Autologous stem cell transplantation for follicular lymphoma: favorable

long-term survival irrespective of pretransplantation rituximab exposure. Biol Blood Marrow Transplant. 2017;23(10):1631-1640.
11. Jurinovic V, Metzner B, Pfreundschuh M, et al. Autologous stem cell transplantation for patients with early progression of follicular lymphoma: a follow-up study of 2 randomized trials from the German Low Grade Lymphoma Study Group. Biol Blood Marrow Transplant. 2018;24(6):1172-1179.
12. Meignan M, Cottereau AS, Versari A, et al. Baseline metabolic tumor volume predicts outcome in high-tumor-burden follicular lymphoma: a pooled analysis of three multicenter studies. J Clin Oncol. 2016;34(30):3618-3626.
13. Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol. 2014;32(27):3059-3068.
14. Barrington SF, Mikhaeel NG, Kostakoglu L, et al. Role of imaging in the staging and response assessment of lymphoma: consensus of the International Conference on Malignant Lymphomas Imaging Working Group. J Clin Oncol. 2014;32(27):3048-3058.
15. Trotman J, Fournier M, Lamy T, et al. Positron emission tomography-computed tomography (PET-CT) after induction therapy is highly predictive of patient outcome in follicular lymphoma: analysis of PET-CT in a subset of PRIMA trial participants. J Clin Oncol. 2011;29(23):3194-3200.
16. Trotman J, Barrington SF, Belada D, et al. Prognostic value of end-of-induction PET response after first-line immunochemotherapy for follicular lymphoma (GALLIUM): secondary analysis of a randomised, phase 3 trial. Lancet Oncol. 2018;19(11):1530-1542.
17. Trotman J, Luminari S, Boussetta S, et al. Prognostic value of PET-CT after first-line therapy in patients with follicular lymphoma: a pooled analysis of central scan review in three multicentre studies. Lancet Haematol. 2014;1(1):e17-e27.
18. Moskowitz AJ, Yahalom J, Kewalramani T, et al. Pretransplantation functional imaging predicts outcome following autologous stem cell transplantation for relapsed and refractory Hodgkin lymphoma. Blood. 2010;116(23):4934-4937.
19. Sauter CS, Matasar MJ, Meikle J, et al. Prognostic value of FDG-PET prior to autologous stem cell transplantation for relapsed and refractory diffuse large B-cell lymphoma. Blood. 2015;125(16):2579-2581.
20. Svoboda J, Andreadis C, Elstrom R, et al. Prognostic value of FDG-PET scan imaging in lymphoma patients undergoing autologous stem cell transplantation. Bone Marrow Transplant. 2006;38(3):211-216.
21. Van Imhoff GW, McMillan A, Matasar MJ, et al. Ofatumumab versus rituximab salvage chemoimmunotherapy in relapsed or refractory diffuse large B-cell lymphoma: the ORCHARRD study. J Clin Oncol. 2017;35(5):544-551.
22. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc. 1958;53(282):457-481.
23. Cox DR. Models and life-tables regression. J R Stat Soc. 1972;34(2):187-202.
24. Kelsey P, Pearce R, Perry J, et al. Substituting carmustine for lomustine is safe and effective in the treatment of relapsed or refractory lymphoma - a retrospective study from the BSBMT (BEAM versus LEAM). Bone Marrow Transplant. 2021;56:730-732.
25. Thomson KJ, Morris EC, Milligan D, et al. T-cell-depleted reduced-intensity transplantation followed by donor leukocyte infusions to promote graft-versus-lymphoma activity results in excellent long-term survival in patients with multiply relapsed follicular lymphoma. J Clin Oncol. 2010;28(23):3695-3700.
26. Leonard JP, Trneny M, Izutsu K, et al. AUGMENT: a phase III study of lenalidomide plus rituximab versus placebo plus rituximab in relapsed or refractory indolent lymphoma. J Clin Oncol. 2019;37(14):1188-1199.
27. Gopal AK, Kahl BS, de Vos S, et al. PI3Kδ inhibition by idelalisib in patients with relapsed indolent lymphoma. N Engl J Med. 2014;370(11):1008-1018.
28. Flinn IW, Miller CB, Ardeshna KM, et al. DYNAMO: a phase II study of duvelisib (IPI-145) in patients with refractory indolent non-Hodgkin lymphoma. J Clin Oncol. 2019;37(11):912-922.
29. Caimi P, Kahl BS, Hamadani M, et al. Safety and efficacy of Adct-402 (loncastuximab tesirine), a novel antibody drug conjugate, in relapsed/refractory follicular lymphoma and mantle cell lymphoma: interim results from the phase 1 first-in-human study. Blood. 2018;132(Suppl 1):2874.
30. Morschhauser F, Tilly H, Chaidos A, et al. Tazemetostat for patients with relapsed or refractory follicular lymphoma: an open-label, single-arm, multicentre, phase 2 trial. Lancet Oncol. 2020;21(11):1433-1442.
31. Budde LE, Assouline S, Sehn LH, et al. Single-agent mosunetuzumab shows durable complete responses in patients with relapsed or refractory B-cell lymphomas: phase I dose-escalation study. J Clin Oncol. 2022;40(5):481-491.
32. Hutchings M, Morschhauser F, Iacoboni G, et al. Glofitamab, a novel, bivalent CD20-targeting T-cell–engaging bispecific antibody, induces durable complete remissions in relapsed or refractory B-cell lymphoma: a phase I trial. J Clin Oncol. 2021;39(18):1959-1970.
33. Schuster SJ, Dickinson MJ, Dreyling MH, et al. Efficacy and safety of tisagenlecleucel (Tisa-cel) in adult patients (Pts) with relapsed/refractory follicular lymphoma (r/r FL): primary analysis of the phase 2 ELARA trial. J Clin Oncol. 2021;39(15 Suppl):7508.
34. Jacobson CA, Chavez JC, Sehgal AR, et al. Axicabtagene ciloleucel in relapsed or refractory indolent non-Hodgkin lymphoma (ZUMA-5): a single-arm, multicentre, phase 2 trial. Lancet Oncol. 2022;23(1):91-103.